REMARKS

Reconsideration of the above application is respectfully requested.

Claims 1-17 are pending in the application. Claims 1-17 have been rejected. Claims 1 and 3-10 have been amended. Claim 2 has been deleted. Specifically, claim 1 has been amended to recite ziprasidone as the aryl heterocyclic compound. Claim 2 has been deleted on the grounds that it is redundant to amended claim 1. Claims 3-10 have been amended to correct claim dependency due to the deletion of claim 2. Applicant herein reserves his right to prosecute the subject matter of original claim 1 in a co-pending divisional application.

The Examiner has rejected claims 1-17 under 35 U.S.C §103(a) as being unpatentable over Kim et al. (US 6,232,304) in view of Greengard et al. (US 2003/0109419) and in view of Yuan et al. (US 5,594,141) on the grounds that although the three references do not anticipate the claims they none-the-less render the claims obvious because Kim discloses arylheteroaryl salts, including ziprasidone, in combination with cyclodextrins, and Greengard discloses combinations of ziprasidone with surfactants such as Tween and polysorbate, and Yuan additionally refers to the inclusion of excipients such as suspending agents including NaCMC for intramuscular injection. The Examiner separately rejects claims 1-17 to the combination of references of Kim and Francois (US 2003/0157180). Furthermore, the Examiner states that it is "prima facie obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose in order to form a composition that is to be used for an identical purpose. The motivation for combining them flows from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose." For the reasons that follow, Applicant respectfully traverses the Examiner's rejection on the grounds that none of the references individually nor taken as a whole teach or suggest that a combination of solubilized ziprasidone with a viscosity agent or an unsolubilized ziprasidone with a viscosity agent and a solubilizing agent could yield a valuable depot formulation with the unexpected properties as described in the present specification.

As the Examiner points out, Kim refers to the combination of arylheteroaryl compounds, including ziprasidone in combination with cyclodextrins. However, as conceded by the Examiner, "Kim is silent on the use of **the two excipients** NaCMC and polyoxyethylene sorbitan ester in the composition" (emphasis added), see page 3 lines 10-11 of the Official Action. Applicant first respectfully traverses the Examiner's characterization of either NaCMC or polyoxyethylene sorbitan ester as "excipients" and respectfully submits that both of these compounds are examples of important elements of the invention. NaCMC is a member of the critical class of "viscosity agents" that are central to the operability of the invention. Trivializing such an element as nothing more than an inert substance added to a formulation to give "form or consistency," (see Stedman's Medical Dictionary, page 547), evidences a complete misunderstanding of the important role this element possesses. Furthermore, linking the viscosity element with the optional surfactant element confirms this confounding. Surfactants such as polyoxyethylene sorbitan ester are optional additions to the present invention see for example page 8, line 37 through page 9 line 1 and page 9

lines 5-8. Coupling such elements is objected to and Applicant respectfully requests that the Examiner furthermore decouple these elements in his rejection. Referring back to the "viscosity agents", Applicant respectfully directs the Examiner to the comparative and unexpected results discussed as Example 4, on page 16 of the specification. Specifically, a formulation of the present invention was compared against an "immediate release formulation comprised of solubilized ziprasidone, but no viscosity agent." Such a comparative formulation (i.e. Kim) "showed no depot effect, i.e. the serum concentration of ziprasidone was not quantifiable after 48 hrs; there was no sustained serum concentration," page 16, lines 12-17. The formulation of the invention on the other hand showed a serum concentration of 12.9+/-3.7 ng/ml. More unexpected comparative results are discussed in the present specification but it is not deemed necessary to go through them all here at this time. Thus, the evidence demonstrates that the addition of a viscosity agent significantly alters the properties of even a solubilized ziprasidone. Addition of the Greengard and Yuan references does not alter the analysis of these surprising results. Greengard, as it relates to the optional additional element of surfactants is not relevant to patentability of the combination of the solubilized or unsolubilized ziprasidone combination with a viscosity agent and is thus dismissed from the rejection rebuttal on these grounds. Since all references to the optional surfactants are predicated on the combination of the solubilized ziprasidone with a viscosity agent the legal application of Greengard is untenable. Interestingly though, this reference arguably teaches away from the present invention because in its listing of formulation agents (including diluents, preservatives, solubilizers, emulsifiers, adjuvants, excipients) no mention of any viscosity agents is made. Furthermore, the reference to the surfactants is made only in the context of solid oral dosage forms. Yuan likewise focuses on oral formulations in the recitation "excipients" in which he links celluloses with flavoring and coloring agents. The injectable formulations are relegated to a minor paragraph on column 12, lines 17-22 and no where in this discussion is made any reference to solubilizing agents or viscosity agents. The addition of Francois does not change the outcome. Francois is directed to the invention of depot forms of risperidone. In this situation the Johnson and Johnson inventors could not even use the parent compound and turned instead to the metabolite of risperidone as their starting material and then derivatized that material into (C_{10}-C_{20})alkanoic 9-hydroxy esters and then combined these prodrugs with a surfactant that was to be "absorbed to the surface thereof," see column 2, paragraph 19. It is hard at the outset to imagine how this reference is applicable to an obvious analysis of the present invention. Contrary to the position of the Examiner, Francois demonstrates the incredible difficulty in creating a useful depot formulation. The inventors in that case couldn't use the active *per se* and had to rely on a metabolite but even the metabolite was not useful enough so they turned to (C_{10}-C_{20})alkanoic 9-hydroxy esters. Even these cumbersome esters were not enough and they then added surfactants that had to be absorbed to the surface of these modified prodrugs. After all of these convolutions then Francois turns to other "conveniently" available additives. It is within this context that the inventors refer to "suspending agents," "buffers," "preservatives" and "isotonizing agents,"

paragraph 42. It is further within the context of "suspending agents" that the Examiner dredges up the reference to celluloses that Applicant includes as a viscosity agent. No where in Francois, in any of the prodrugs, metabolites, surfactants and surface absorbances is there any mention of anything remotely related to viscosity or the use of viscosity agents. If anything this reference teaches strongly away from the present invention in its elegant but convoluted conversion of the risperidone. After all of these steps the Examiner would have one of ordinary skill in the art look to essentially a footnote as the foundation of an obviousness argument. Applicant respectfully submits that such strained analysis is completely inappropriate to the proper legal standard of obviousness. Even the recent Supreme Court holding in KSR International Co. v. Teleflex, Inc. 82 USPQ2d 1385 (US Supreme Ct 2007) does not go as far as the Examiner. The court stated that whether there was a "reason" to combine known elements as combined by a patentee a court will often have to look to (1) interrelated teachings of multiple patents; (2) the effects of demands known to the design community or present in the marketplace; and (3) the background knowledge possessed by a person having ordinary skill in the art. Although this analysis should be explicit, the court explained, it "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." The Examiner has not provided any such analysis other than a disconnected patchwork of references that recite laundry lists of "excipients." Finally, the USPTO still maintains that "in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed," see Deputy Commissioner Focarino's PTO Staff Memo, May 3, 2007. In light of the foregoing, Applicant is left to wonder where the motivation lies to add a viscosity agent to a solubilized ziprasidone or add a viscosity agent and a solubilizing agent to an unsolubilized ziprasidone. Is the Examiner really taking the position that formulation science is no longer patentable subject matter in the United States because one can always find a group of references that taken together lists all of the myriad elements used in formulations? Applicant respectfully submits that the law is otherwise and no such motivation to combine exists and requests that the Examiner withdraw the § 103 rejection.

The Examiner has applied the same references specifically to claims 11, 12 and 15. Applicant respectfully submits that for the reasons detailed above that these claims are not obvious in light of the cited references taken individually or as a whole.

In conclusion, Applicant submits that all pending claims are patentable, and respectfully request that they be allowed to issue.

Respectfully submitted,

Date: June 8, 2007

/Garth Butterfield/
Garth Butterfield
Attorney for Applicant
Reg. No. **36,997**

Pfizer Inc.
Patent Dept., 150-5-49
235 East 42nd Street
New York, NY 10017-5755
(212) 573-**1229**

Stedman's

MEDICAL DICTIONARY

25th Edition

ILLUSTRATED

STEDMANS

Editor: William R. Hensyl
Associate Editor: Harriet Felscher
Administrative Assistant: Julie Rodowsky
Administrative Aide: Gertrude A. Wilder

Project Editor: Bill Cady
Designer: Robert C. Och
Illustration Planner: Wayne J. Hubbel
Production Coordinator: Raymond E. Reter

Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

Printed in the United States of America

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985
Portuguese 1976
Spanish (in press)

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853–1938.
[Medical dictionary]
Stedman's medical dictionary.—25th ed.
p. cm.
ISBN 0-683-07916-6
1. Medicine—Dictionaries. I. Title. II. Title: Medical dictionary
[DNLM: 1. Dictionaries, Medical. W 13 S812m]
R121.S8 1989
610'.3—dc20
DNLM/DLC
for Library of Congress

89-16579
CIP

90 91 92 93 94
2 3 4 5 6 7 8 9 10

excementosis (ek'se-men-to'sis). A nodular outgrowth of cementum on the root surface of a tooth.

excentric (ek-sen'trik). Alternative spelling for eccentric (2, 3).

excess (ek'ses). That which is more than the usual or specified amount.

antibody e., in a precipitation test, the presence of antibody in an amount greater than that required to combine with all of the antigen present.

antigen e., **(1)** in a precipitation test, the presence of uncombined antigen above that required to combine with all of the antibody; precipitation may be inhibited because the presence of excess antigen gives rise to soluble antigen-antibody complexes; **(2)** *in vivo,* the resultant antigen-antibody interaction in such an antigen e. may give rise to immune complexes, which have a potential to induce cellular damage; such injury underlies the pathologic changes seen in certain immune complex diseases.

base e., a measure of metabolic alkalosis, usually predicted from the Siggaard-Andersen nomogram; the amount of strong acid that would have to be added per unit volume of whole blood to titrate it to pH 7.4 while at 37°C and at a carbon dioxide pressure of 40 mm Hg.

convergence e., that condition in which an esophoria or esotropia is greater for near vision than for far vision.

negative base e., a measure of metabolic acidosis, usually predicted from the Siggaard-Andersen nomogram; the amount of strong alkalai that would have to be added per unit volume of whole blood to titrate it to pH 7.4 while at 37°C and at a carbon dioxide pressure of 40 mm Hg.

exchange (eks-chānj'). To substitute one thing for another, or the act of such substitution.

sister chromatid e., the e. during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

excipient (ek-sip'ē-ent) [L. *excipiens;* pres. p. of *ex- cipio,* to take out]. A more or less inert substance added in a prescription as a diluent or vehicle or to give form or consistency when the remedy is given in pill form; *e.g.,* simple syrup, aromatic powder, honey, and various elixirs.

excise (ek-sīz'). Exsect; to cut out. See also resect.

excision (ek-sizh'ŭn) [L. *excidere,* to cut out]. **1.** Exsection; exeresis; the act of cutting out; the surgical removal of part or all of a structure or organ. See also resection. **2.** In molecular biology, a recombination event in which a genetic element is removed.

excitability (ek-sī'tă-bil'i-te). Having the capability of being excitable.

supranormal e., at the end of phase three of the cardiac action potential, the successful stimulation threshold falls below the level necessary to produce excitation during the rest of the phase of diastole, so that an ordinary subthreshold stimulus becomes effective. *Cf.* supranormal *conduction.*

excitable (ek-sī'tă-bl). **1.** Capable of quick response to a stimulus; having potentiality for emotional arousal. *Cf.* irritable. **2.** In neurophysiology, referring to a tissue, cell, or membrane capable of undergoing excitation in response to an adequate stimulus.

excitant (ek-sī'tănt) [L. *excito,* pp. *-atus,* pres. p. *-ans,* to arouse]. Stimulant.

excitation (ek-sī-ta'shŭn). **1.** The act of increasing the rapidity or intensity of the physical or mental processes. **2.** In neurophysiology, the complete all-or-none response of a nerve or muscle to an adequate stimulus, ordinarily including propagation of e. along the membranes of the cell or cells involved. See also stimulation.

excitatory (ek-sī'tă-to-re). Tending to produce excitation.

excitement (ek-sīt'ment). An emotional state characterized by its potential for impulsive or poorly controlled activity.

catatonic e., an excited catatonic state. See catatonia.

manic e., an excited mental state characterized by hyperactivity, talkativeness, flight of ideas, pressured speech, grandiosity, and, occasionally, grandiose delusions.

excitoglandular (ek-sī'tō-glan'dyū-lăr). Increasing the secretory activity of a gland.

excitometabolic (ek-sī'tō-met-ă-bol'ik). Increasing the activity of the metabolic processes.

excitomotor (ek-sī'tō-mō'ter). Centrokinetic (2); causing or increasing the rapidity of motion.

excitomuscular (ek-sī'tō-mŭs'kyū-lăr). Causing muscular activity.

excitor (ek-sī'ter, -tōr). Stimulant (2).

excitosecretory (ek-sī'tō-sē-kre'tō-rē). Stimulating to secretion.

excitovascular (ek-sī'tō-vas'kyū-lăr). Increasing the activity of the circulation.

exclave (eks-klāv') [L. *ex,* out, + *-clave* (in enclave, *q.v.*)]. An outlying, detached portion of a gland or other part, such as the thyroid or pancreas; an accessory gland.

exclusion (eks-klū'zhŭn) [L. *ex- cludo,* pp. *-clusus,* to shut out]. A shutting out; disconnection from the main portion.

allelic e., in each cell of an individual heterozygous at an autosomal locus, the non-preferential supression of the phenotypic manifestation of one or other of the alleles; the phenotype of the body is thus mosaic.

Devine e., e. of the lower part of the stomach, followed by gastrojejunostomy, for treatment of duodenal ulcer.

e. of pupil, seclusion of pupil; the condition resulting from posterior annular synechia, in which the iris is bound down throughout the entire pupillary margin, but the pupil is not occluded.

exconjugant (eks-kon'ju-gant) [ex- + L. *conjugo,* to join]. A member of a conjugating pair of protozoan ciliates after separation and prior to the subsequent mitotic division of each of the e.'s. See also conjugant; conjugation (3).

excoriate (eks-ko'rē-āt). To scratch or otherwise denude the skin by physical means.

excoriation (eks-kō'rē-ā'shŭn) [L. *excorio,* to skin, strip, fr. *corium,* skin, hide]. A scratch mark; a linear break in the skin surface, usually covered with blood or serous crusts.

neurotic e., repeated self-induced e., with or without underlying skin lesions, associated with compulsive or neurotic behavioral problems.

excrement (eks'krē-ment) [L. *ex- cerno,* pp. *-cretus,* to separate]. Waste matter or any excretion cast out of the body; *e.g.,* feces.

excrementitious (eks'krē-men-tish'ŭs). Relating to any excrement.

excrescence (eks-kres'ens) [L. *ex- cresco,* pp. *-crētus,* to grow forth]. Any outgrowth from a surface.

excreta (eks-kre'tă) [L. neut. pl. of *excretus,* pp. of *ex-cerno,* to separate]. Excretion (2).

excrete (eks-krēt'). To separate from the blood and cast out; to perform excretion.

excretion (eks-krē'shŭn) [see excrement]. **1.** The process whereby the undigested residue of food and the waste products of metabolism are eliminated, material is removed to regulate the composition of body fluids and tissues, or substances are expelled to perform functions on an exterior surface. **2.** Excreta; the product of a tissue or organ that is material to be passed out of the body. *Cf.* secretion.

excretory (eks-kre'to-re). Relating to excretion.

excursion (eks-ker'zhŭn). Any movement from one point to another, usually with the implied idea of returning again to the original position.